

Subvalvular Calcification of Mitral Valve

R. S. KIRK AND J. G. B. RUSSELL

From the Department of Pathology, University of Manchester and Department of Radiology, Manchester Royal Infirmary

The pathological processes that develop in the heart with ageing are numerous. One of these processes is mitral ring calcification (Fertman and Wolff, 1946; Geill, 1951). It occurs frequently and has been variously ascribed to rheumatic disease, rheumatoid disease, and endocarditis of various aetiologies; it is more generally regarded as an end-stage degenerative disorder similar to the Mönckeberg type of aortic valve calcification.

In a study of adult hearts we have found that calcification in the region of the mitral ring occurs more frequently than is generally recognized, and that in many hearts the site of calcification is mainly in the subvalve angle or recess of the mitral valve and not in the true valve ring. Our studies have shown that this type of calcification occurs in organizing thrombi which can be demonstrated in the subvalve recess.

SUBJECTS AND METHODS

In the course of a study of cardiac calcification (Russell and Kirk, 1966), 194 hearts were examined in a consecutive series of necropsies, excluding cases under the age of 20.

For the radiological examination of the hearts, the ventricles were opened anteriorly close to the ventricular septum, and at least one radiograph was exposed with the left ventricle spread open. This view has the advantage that the mitral and aortic valves are clearly shown, and displays the subvalvular recess so that it is seen along its whole length. The hearts were examined macroscopically, and pathological abnormalities noted, with special reference to the valve and valve ring. Standard blocks were taken for microscopy, including at least one section through the posterior cusp of the mitral valve, with adjacent left atrial and left ventricular myocardium.

Using these methods, 24 hearts from the 194 (12.4%) were found to have calcification in the region of the mitral valve ring (Table). Radiology revealed several cases of early calcification, which had not been discovered at

routine necropsy. Of these 24, 22 had calcification in the mitral subvalve angle.

ANATOMY

Normal Anatomy of Mitral Valve and Ring. The mitral valve consists of two thin, tough, pliable leaflets, the anterior and posterior, which are attached at their base to the mitral annulus. They are held in position by three groups of chordae tendineae (Brock, 1952). The first and second groups are inserted into the papillary muscles, the first arising from the cusp margins and the second from the ventricular surfaces just proximal to the margins; the third group, which are only present on the posterior cusp, run from the left ventricular wall to the cusp just distal to the junction between cusp and ring. Indeed some are merely fibrous folds with no hiatus, rather than free-running chordae.

The mitral ring is part of the fibrous skeleton of the heart, and must be considered in relation to it. The mitral ring is attached to the left and right fibrous trigone, and from it arise the bundles of ventricular myocardium which interweave to form the ventricular walls. The annulus is usually divided into two parts: the antero-medial part forming one-third, and a postero-lateral portion forming two-thirds of the ring. The antero-medial portion gives origin to the anterior mitral cusp and also to part of the aortic valve ring, though separated by an intervalvular septum (Du Plessis and Marchand, 1964). The postero-medial part gives origin to the posterior cusp. The mitral valve has an important relation to the left ventricular outflow tract (Walmsley and Watson, 1966). The posterior cusp lies in relation throughout its length to the postero-lateral wall of the left ventricle; whereas much of the anterior cusp forms the lower posterior wall of the aortic outflow tract (Fig. 1).

Received April 16, 1968.

TABLE
AGE IN YEARS AT DEATH OF 194 CASES

	20-34		35-44		45-54		55-64		65-74		Over 75		Totals		Both sexes
	M	F	M	F	M	F	M	F	M	F	M	F	M	F	
Total no.	6	3	8	5	20	15	29	21	32	25	13	17	108	86	194
No. with calcification in region of AV ring	—	—	—	—	1	—	1	3	1	7 (28%)	4 (31%)	7 (41%)	7 (6.5%)	17 (20%)	24 (12.4%)

Mean age of men: 60 years.
Mean age of women: 56.5 years

RADIOLOGICAL ANATOMY

In life the mitral ring lies in a plane, a perpendicular to which points downward, forward, and to the left, i.e. looking towards the cardiac apex. The subvalve angle is close to the mitral ring, lying nearer the cardiac apex. While the mitral ring is complete, the recess of the subvalve angle is incomplete, as noted, for the recess is not present in the region of the aortic outflow tract. Thus, calcification in the mitral subvalve angle can never appear as a ring but is seen as a C or J shape, the open part of the incomplete circle lying at the site of the aortic outflow tract above and anterior to the calcification (Fig. 2). However, first, often only part of the subvalve angle is involved. In this case the most

usual site is under the posterior mitral leaflet, so that it appears as a small section of arc. This position was noted by Geill (1951) to be usually the initial site of calcification in the mitral ring. On the postero-anterior film the medial part overlies the spine, and the lateral part overlies the main left lower lobe arteries, so that it can be easily missed. However, the lateral view shows calcification clearly (Fig. 3). On screening the heart, the subvalve angle calcification is opened out best in the left anterior oblique position and moves only slightly with systole. Care must be taken not to confuse it with calcification in the left coronary artery running in the atrioventricular groove. We have found stroboscopic tomography (Russell, 1964) useful in determining the extent during life.

The post-mortem x-ray of the heart shows subvalve angle calcification as a dense shadow varying

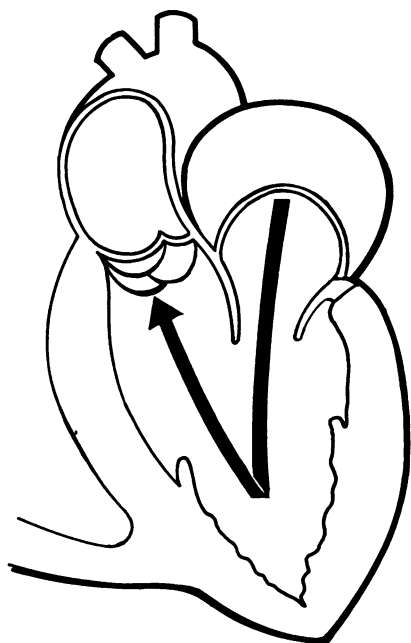


FIG. 1.—Diagram of a section of left ventricle, showing the relation of the aortic outflow tract to the mitral valve. Note the subvalve angle between the posterior mitral cusp and the ventricular myocardium.

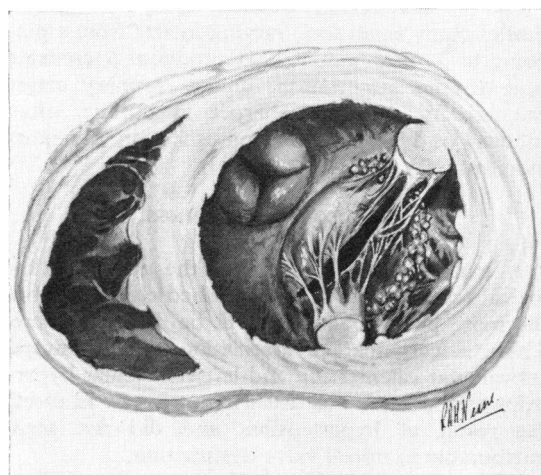


FIG. 2.—View of subvalvular calcification. The posterior cusp of the mitral valve has been lifted up into the valve orifice, exposing the subvalvular angle which is filled with the irregular, calcified mass, extending along the whole of the subvalvular angle of the posterior cusp, and extending to the anterior cusp. No calcification is seen in the region of the aortic outflow tract.

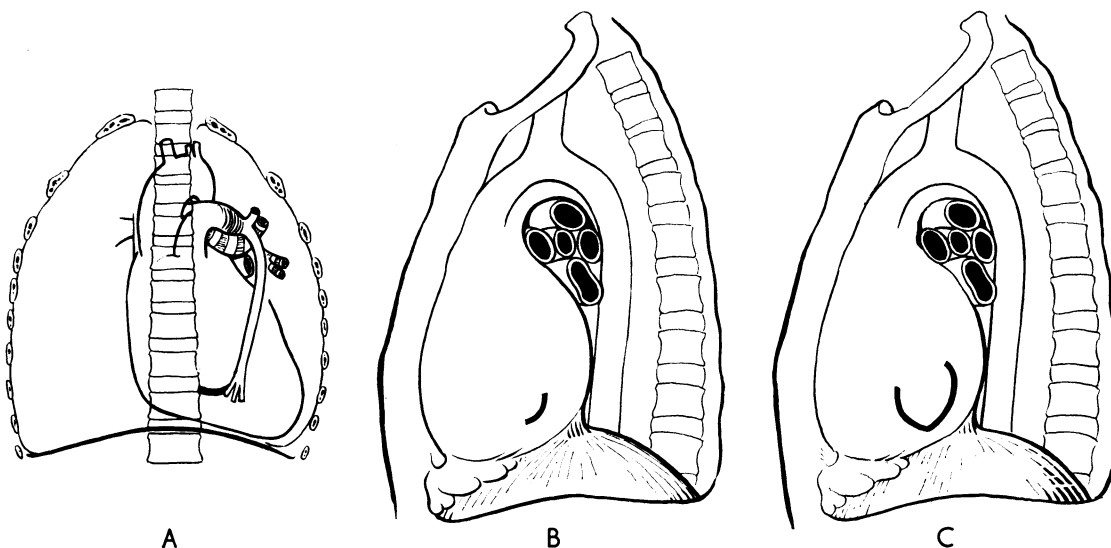


FIG. 3.—Diagrams to show the radiological appearance of mitral subvalvular calcification. On the postero-anterior film early calcifications are not visible. In more severe cases only a segment of the calcification is seen (A), as it is hidden otherwise by the descending bronchovascular bundle laterally, and the spine medially. In a lateral view the appearances of a minor involvement of a small segment, under the posterior cusp, are seen in (B), and the findings with an extensive involvement in (C).

in length from a few mm. to 8 cm., and in breadth from less than 1 mm. to 1 cm., tapering towards the ends. In its early stage it may be in several positions which coalesce later. Close examination shows that it appears to be made up by the aggregation of many small foci, varying in size from a pinpoint to 3 or 4 mm. This produces a crenated edge to the calcification, unlike coronary artery calcification, which is sharper in outline, often tubular, and is easily distinguished on the post-mortem x-ray.

PATHOLOGICAL FINDINGS

A more detailed analysis of the clinico-pathological association will be published elsewhere, but the more pertinent results will be described here. There is very marked association between mitral subvalvular calcification and left ventricular hypertrophy; this latter was usually (but not in all cases) the result of hypertension, and did not seem attributable to mitral valve dysfunction.

Of the 17 women with mitral subvalvular calcification, 4 had clinically diagnosed diabetes mellitus, and since there were only 7 cases of diabetes among the women in the series, this means that more than half of the female diabetics showed mitral subvalvular calcification. It is of interest that in 2 of them the major portion of the calcification was within the

true annulus and there was only minimal involvement of the subvalve angle. Out of the total of 24 patients, 6 (including 2 with diabetes) had pulmonary emboli, associated with various other conditions such as the post-operative state and rheumatic heart disease; 4 (including 2 with diabetes) had associated cerebral or cerebellar infarction. There was no increase in the incidence of rheumatic heart disease above that found in the rest of the series. Only 1 patient showed evidence suggestive of a previous bacterial endocarditis; this was in the tricuspid valve where there was scarring and thickening of the cusp with focal calcification.

From the continuous series 24 patients with mitral ring calcifications were collected, 17 women and 7 men. Additional cases have been examined and reviewed and they support the findings in this series. The age distribution as compared with the general series is shown in the Table.

The Table also gives the incidence expressed as a percentage of the post-mortem population, showing a much increased incidence with age; more so than has been previously reported.

The calcification was identified radiologically and its size and distribution were recorded. No attempt was made in this survey to search for sites of microscopical calcification (Sell and Scully, 1965). The lesion was graded into two groups, *mild* and *severe*; the *mild* group involved only a portion of the pos-



FIG. 4.—Extensive subvalvular calcification under the posterior cusp of the mitral valve which has been lifted up to show it. Note the numerous excrescences of the mass.

terior ring, and the *severe* showed a solid bar of calcification at least involving the whole of the posterior ring. There were no cases of *severe* calcification in men.

The calcification noted radiologically develops in the subvalve pocket anywhere along the junction between cusp and wall. It is usually covered by endocardium but even when small in extent it is in close relation to the ventricular cavity. It may involve up to a third of the extent of the posterior ring as a thin plate of calcium, but frequently before it is as large as this it shows nodular excrescences jutting out into the ventricular cavity (Fig. 4). Where it comes into contact with the third group of chordae it may extend along these for a few millimetres. The calcific deposit can increase in size until it forms a solid bar up to 2 cm. in diameter extending round below the posterior cusp and ending usually abruptly at the lateral commissure. In 3 of the 5 cases showing severe calcification the calcific bar extended round the lateral commissure and involved a small portion of the anterior cusp at the point where there is a recess from the main outflow tract. This recess has been well shown by Walmsley and Watson (1966), whose Fig. 2 shows that the anterior part of the anterior cusp curves at right angles to the main outflow.

It is difficult in the early stages to determine the exact site of calcification, whether it is within the valve ring or whether it is occurring in thrombosis; and, where there is calcified tissue in both places, to identify which has been involved primarily. It

is undoubtedly true that calcification to a greater or lesser extent can occur within the true valve ring, and the calcification can be so extensive as to be visible through, and to lift up, the endocardium of the left atrium. Similarly, it can extend to involve the interventricular septum (which is in direct continuity with the mitral annulus); it may penetrate and extend into the myocardium of the left ventricle; and it can (when it becomes a thick bar in the subvalve angle) become adherent to and partially involve the posterior cusp of the mitral valve.

However, in the present series only two hearts showed a strip of calcified tissue sufficiently thin to be classified as involving the annulus alone. In only one of these cases did the calcification spread to involve structures other than the subvalve angle. In the remaining 22 cases there was prominent involvement of the subvalve angle, and of these, 7 showed extensive spread to other structures.

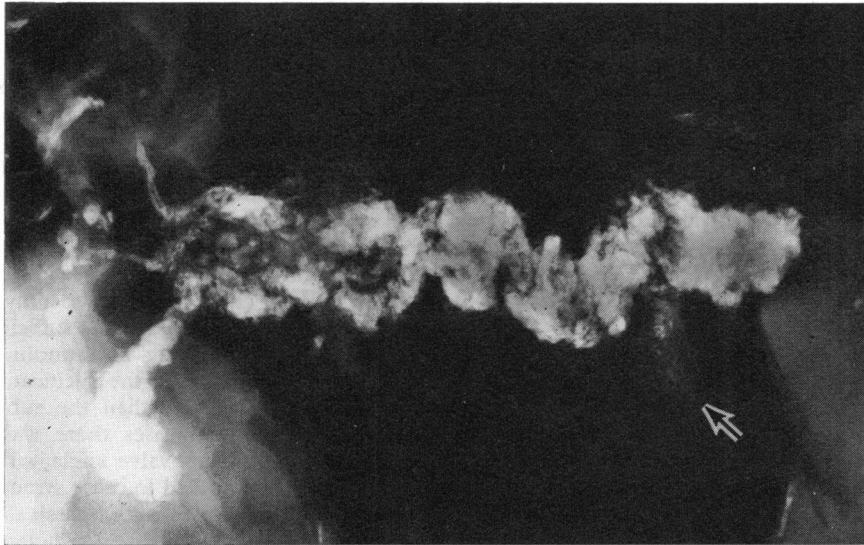
In one of our cases with massive calcification there were numerous thrombi adherent to the inferior surface of the calcific bar, and many of these (including one large pedunculated thrombus) showed calcification occurring within the thrombi and separated from the main calcific mass (Fig. 5): in this case there was very little calcification extending into the ring, but there was some calcification of the interventricular fibrous septum.

CLINICAL FINDINGS

When the subvalvular calcific bar becomes mas-



(A)



(B)

FIG. 5.—Naked eye appearance (A) and post-mortem x-ray film (B) of subvalvular calcification. The posterior cusp of the mitral valve has been lifted up to display the subvalve angle. Uncalcified thrombus is laid down along the ventricular surface, and one pedunculated growth (arrow) of thrombus shows spots of calcification within it.

sive, the ring is rigid and the posterior mitral cusp is stretched tautly over the calcific bar. It will be recognized that this can cause cardiac murmurs, and that it can cause mitral stenosis or incompetence. An illustrative case is presented.

ILLUSTRATIVE CASE

B.P., a woman of 67, weighed 106.6 kg. (235 lb.). She gave a history of rheumatic fever at the age of 12. She had had a cholecystectomy at 57 years, but had recently developed symptoms of biliary colic. On ad-

mission for surgical exploration of her bile-ducts, she was found to have a hypertension of 185/105 mm. Hg. There was a loud diastolic murmur maximal at the apex, but also heard in the aortic area. The chest x-ray film (Fig. 6) showed a normal heart size, with no significant left atrial enlargement, but there was a curvilinear calcification around the mitral valve area. This is seen well on the stroboscopic tomogram (Fig. 7).

A clinical diagnosis of mitral stenosis was made. Choledochostomy was performed, but she died suddenly on the fourth post-operative day. At necropsy the cause of death was established as a massive pulmonary embolus arising from the deep veins of the calves. She also had a small middle fossa meningioma. The heart weighed 380 g. The left ventricle was hypertrophied. The coronary arteries showed severe atherosclerosis, with narrowing of the lumen to two-thirds of its original diameter. The mitral valve annulus was calcified and there was a prominent subvalvular bar of calcific tissue involving the lateral two-thirds of the posterior cusp and tapering to involve 0.3 cm. of the anterior cusp. At the latter point it was adherent to the undersurface of the commissure and not attached to the annulus. At its other end (under the medial part of the posterior commissure) it penetrated the myocardium and extended as a rod, 1.2 cm. in diameter, which extended for 2 cm. where it tapered to a point. It did not reach the inter-ventricular septum.

The post-mortem x-ray film (Fig. 8) shows clearly the extent of the severe subvalvular calcification involving the whole subvalvular recess.

DISCUSSION

We contend that the so-called condition of mitral ring calcification is a misnomer in the sense that,

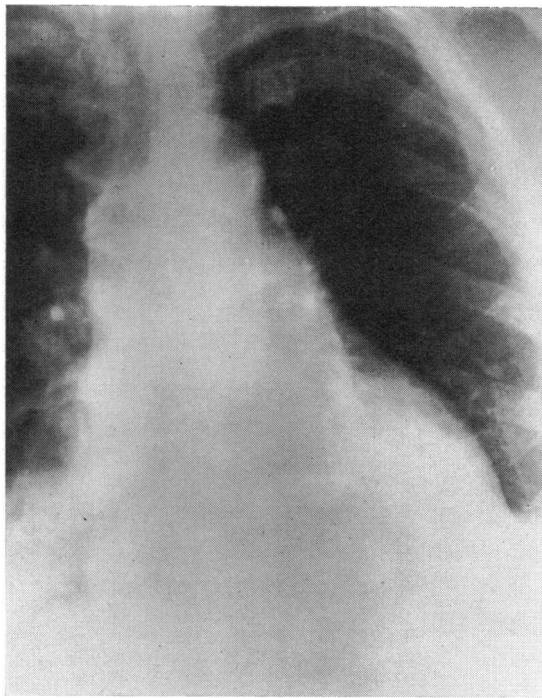


FIG. 6.—Postero-anterior chest x-ray film shows the subvalvular calcification visible within the large heart.

in most cases, the major portion of the calcification lies in the subvalve angle protruding into the ventricular cavity. Propagation and increase in size

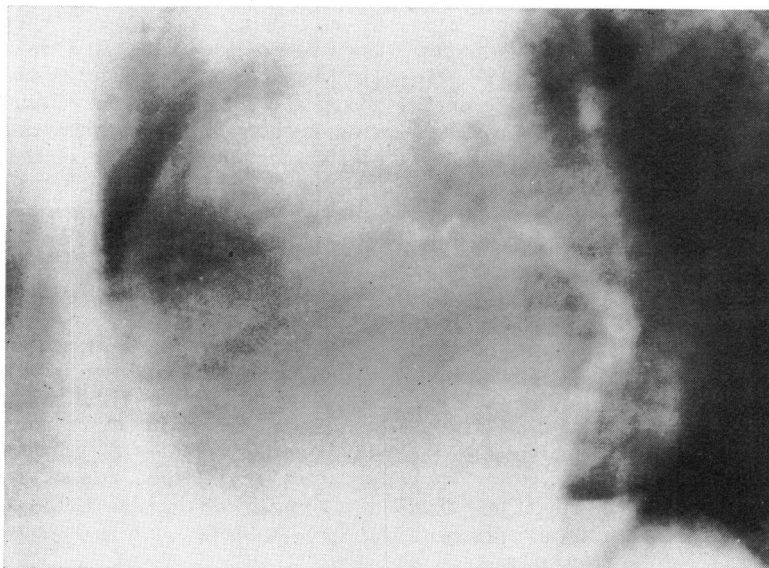


FIG. 7.—Stroboscopic tomogram, exposed in a left lateral projection, showing the calcification in the mitral subvalvular angle. Only the posterior part of it is in focus on this tomographic cut.

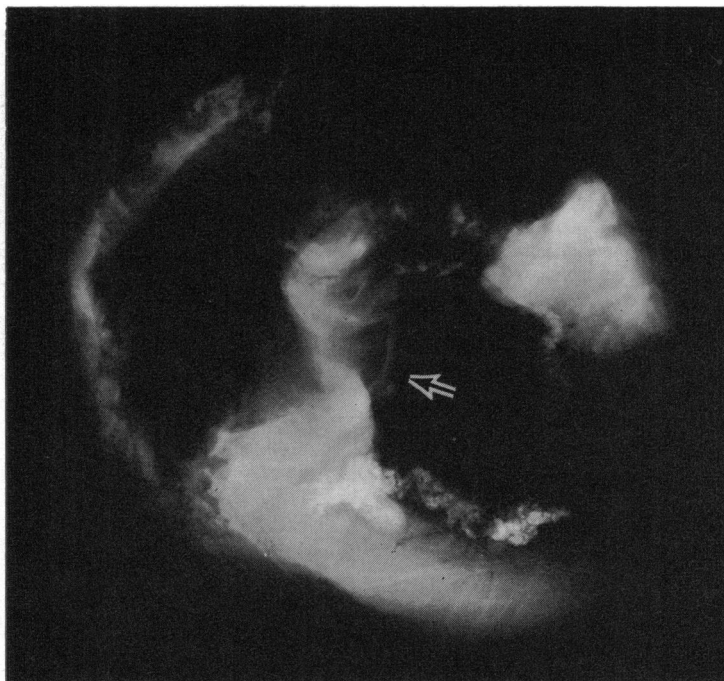


FIG. 8.—Post-mortem x-ray film of the heart. The ventricles have been opened and are viewed looking down through the mitral and tricuspid valves. The thick walled left ventricle shows within it the subvalvular calcification. It is incomplete in the area of the aortic outflow tract (arrow).

may occur as the result of thrombus deposition, so that the process is of an accretive nature rather than a true degenerative disorder. Thus, there is an analogy with the thrombogenic theory of atheroma (Duguid, 1946; Crawford and Levene, 1952). In the stenosing type of atheroma the surface of the thrombus becomes endothelialized and the thrombus undergoes hyalinization and sometimes calcification. We have not been able to find any previous report showing that subvalvular thrombus occurs, though Hudson (1965) suggests it as a possibility.

The site of the subvalve calcification is one where stasis of blood might occur. Stasis will not occur in the outflow tract of the left ventricle. It has been suggested that the posterior cusp of the mitral valve often moves only slightly during systole and diastole, and that the anterior cusp performs most of the closure of the mitral valve surface (Brock, 1952), which may be an element promoting stasis in the subvalve angle of the posterior cusp.

It has been shown (Sell and Scully, 1965) that, with age, changes occur in the mitral valve ring, with accumulation of lipid and microscopical foci of calcification. It may be that these age changes in the subendocardium are a necessary precursor, and

that they act as a focus for the deposition of thrombus. But such histological changes can also occur in thrombi in atheromatous plaques, and in thrombi occurring on the mitral valve cusps in mitral stenosis (Magarey, 1949). In our opinion, many of these changes occur outside the original fibrous valve ring, in thrombi, and the valve ring can increase in size through incorporation of these thrombi. In only two of our cases did it seem possible that the calcification was entirely restricted to the ring with no subvalve extensions. In both these cases there was no left ventricular hypertrophy and the calcification was short and only involved part of the posterior cusp ring.

Our findings offer an explanation for the incomplete circle of calcification which occurs; intra-thrombal calcification cannot occur where the subvalve angle is absent at the aortic outflow tract. Previous authors have described the shape as an arc, U, C, or J shaped, and all say that only rarely is a complete circle seen. We have not been able to find an illustration of a case showing a complete circle of calcification.

Various theories have been proposed to explain this; one such (De Oliveira, 1943) suggested that

collagen degeneration (as a precursor to calcification) did not occur in the anterior ring because it was more cellular. Yater and Cornell (1935) have pointed out that the lesion occurs at the point of maximum stress and strain in the left ventricle, and they thought that decreased blood supply might be an important factor in its genesis. In the present series there is a significant association of subvalve calcification with left ventricular hypertrophy; increased stress is probably an important aetiological factor. Davis and Kinmonth (1963) showed that contraction of the circumference of the mitral annulus occurred over the lateral aspect and not in the region of the aortic root or fibrous trigone.

Thrombi can develop within the cardiovascular system if there is endothelial damage, if there is stasis of blood, or if there is an alteration in the clotting mechanisms. There is probably little stasis in the left ventricle in the normal heart, but it may be that with dilatation and incomplete emptying thrombi can develop in the subvalve angle. If the mitral ring dilates when the heart enlarges, the excursion of the mitral cusps must increase. This might tend to tear the fibrous chordae tendineae of Brock's third group, and thus cause focal endothelial damage, on which platelet deposition might start.

Various other theories have been advanced on the aetiology of mitral valve ring calcification. It cannot be correlated with coronary artery sclerosis (Simon and Liu, 1954). The preponderance of women in all the published series has given rise to the suggestion that there may be an endocrine basis.

Because of the reported association with senile osteoporosis (Ipsen, 1934; Geill, 1951), it has been suggested that mobilization of calcium may result in the deposition of calcium in the mitral valve ring and other organs; but it has been shown that the serum calcium and phosphate levels are not altered in osteoporosis so this is probably a fortuitous association. Martens (1932) has emphasized the frequent occurrence of hyperostosis frontalis and calcification of intervertebral discs in association with mitral annulus calcification. Several of the cases described by Rytand and Lipsitch (1946) had raised plasma proteins and cholesterol.

It may be relevant that in the present series there is a greatly increased incidence of diabetes. Though many of our cases showed intravascular thrombotic lesions of various types, such as pulmonary embolism or cerebral infarction, these were probably terminal events occurring in association with heart failure or as a post-operative complication.

As calcification in or near the annulus is so frequently unrecognized until after death, we must assume that mild degrees produce little or no symptoms. However, when it becomes more

severe and develops into the subvalvular type which we are describing, then valvular dysfunctions can develop. Systolic murmurs concomitant with mitral incompetence have frequently been noted to occur as the result of a rigid dilated mitral valve ring (Simon and Liu, 1954). It has been shown (Kantrowitz, Hurwitt, and Herskovitz, 1952; Davis and Kinmonth, 1963) that a sphincteric action of the mitral ring contributes to effective closure of the mitral valve; and obviously rigidity through calcification would interfere with such an action. The possibility of calcification in this region causing mitral stenosis has been considered rare but has been clearly demonstrated (Korn, DeSanctis, and Sell, 1962). This arises as a result of the calcified bar narrowing the mitral orifice. The cusps may be thickened and partially incorporated. If patients have calcification severe enough to cause stenosis they may also have an incompetence, due to the loss of sphincteric contraction.

The calcification in addition to occupying the subvalvular area can also spread to involve the inter-ventricular fibrous septum and, if extensive enough, the ventricular myocardium. This extension of calcification within the heart to adjacent structures is well recognized (Kirk and Russell, 1966).

Two aspects of this subvalvular calcification are unexplained. The first problem is its predilection for the left ventricle; it has never been described in the right ventricle. This most probably is related to the greater stresses and pressures that are sustained by the left ventricle. The second problem is to explain why the mass calcifies. It is well known that atheromatous plaques may undergo calcification as also do thrombi; but the bar of new "tissue" in the mitral subvalve angle, though having a rim of hyaline acellular tissue, is almost completely calcified. Thrombi in the subvalve angle are attached to a relatively avascular valve ring and are subject to a widely fluctuating pressure. It can only be assumed that thrombi in this site, being subject to variable pressures, are more prone to calcify.

SUMMARY

Using a combined pathological and radiological approach we found that calcifications in the region of the mitral valve ring were shown more frequently than previous observation had suggested. In 194 hearts at necropsy there were 2 cases with calcification confined to the mitral valve ring. In 22 instances calcification was present in the mitral subvalve angle, and occurred in relation to thrombosis at this site. The associated clinical findings are described.

We would like to thank Professor A. C. P. Campbell of the Department of Pathology for helpful advice, and Dr. R. Ollerenshaw of the Department of Medical Illustration, Manchester Royal Infirmary, and Mr. R. Neave, Medical Artist, for the illustrations.

REFERENCES

- Brock, R. C. (1952). The surgical and pathological anatomy of the mitral valve. *Brit. Heart J.*, **14**, 489.
- Crawford, T., and Levene, C. I. (1952). The incorporation of fibrin in the aortic intima. *J. Path. Bact.*, **64**, 523.
- Davis, P. K. B., and Kinmonth, J. B. (1963). The movements of the annulus of the mitral valve. *J. cardiovasc. Surg. (Torino)*, **4**, 427.
- De Oliveira, R. M. (1943). *Escleroses Valvulares Calcificadas*. Patronato, Rio de Janeiro.
- Duguid, J. B. (1946). Thrombosis as a factor in the pathogenesis of coronary atherosclerosis. *J. Path. Bact.*, **58**, 207.
- Du Plessis, L. A., and Marchand, P. (1964). The anatomy of the mitral valve and its associated structures. *Thorax*, **19**, 221.
- Fertman, M. H., and Wolff, L. (1946). Calcification of the mitral valve. *Amer. Heart J.*, **31**, 580.
- Geill, T. (1951). Calcification of the left annulus fibrosus. *J. Geront.*, **6**, 327.
- Hudson, R. E. B. (1965). *Cardiovascular Pathology*. Edward Arnold, London.
- Ipsen, J. (1934). Om petrificatio annuli fibrosi mitralis. *Nord. med. T.*, **8**, 1004.
- Kantrowitz, A., Hurwitt, E. S., and Herskovitz, A. (1952). A cinematographic study of the function of the mitral valve in situ. *Surg. Forum*, **1951**, **2**, 204.
- Kirk, R. S., and Russell, J. G. B. (1966). Spiral calcification in the ventricular myocardium. *Brit. Heart J.*, **28**, 342.
- Korn, D., DeSanctis, R. W., and Sell, S. (1962). Massive calcification of the mitral annulus. *New Engl. J. Med.*, **267**, 900.
- Magarey, F. R. (1949). On the mode of formation of Lambl's excrescences and their relation to chronic thickening of the mitral valve. *J. Path. Bact.*, **61**, 203.
- Martens, G. (1932). Beziehungen zwischen der Verkalkung des Annulus fibrosus der Mitralklappen und anderen regressiven Erscheinungen. *Beitr. path. Anat.*, **90**, 497.
- Russell, J. G. B. (1964). Stroboscopic tomography of the heart. *Brit. J. Radiol.*, **37**, 440.
- , and Kirk, R. S. (1966). Cardiac Calcifications. Paper delivered to the Spring Meeting, Faculty of Radiologists.
- Rytand, D. A., and Lipsitch, L. S. (1946). Clinical aspects of calcification of the mitral annulus fibrosus. *Arch. intern. Med.*, **78**, 544.
- Sell, S., and Scully, R. E. (1965). Aging changes in the aortic and mitral valves. *Amer. J. Path.*, **46**, 345.
- Simon, M. A., and Liu, S. F. (1954). Calcification of the mitral valve annulus and its relation to functional valvular disturbance. *Amer. Heart J.*, **48**, 497.
- Walmsley, R., and Watson, H. (1966). The outflow tract of the left ventricle. *Brit. Heart J.*, **28**, 435.
- Yater, W. M., and Cornell, V. H. (1935). Heart block due to calcareous lesions in the bundle of His. *Ann. intern. Med.*, **8**, 777.